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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,966	09/11/2003	Richard B. Roth	SEQ-4038-UT	9006

47328 7590 09/18/2006

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,966	ROTH ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5-9,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/2006, 6/2004*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1, and a polymorphism at position 146311 in SEQ ID NO: 1, and SEQ ID NO: 45 for claim 14, in the reply filed on 6/30/2006 is acknowledged. The traversal is on the ground(s) that that the election of the polymorphism and the oligonucleotide sequence should not be a requirement for restriction but instead a species election. With regard to the restriction between the polymorphisms as recited in claim 1, it is noted that claim 1, directed to SEQ ID NO: 1, is linking with regard to the polymorphisms listed in claim 3, for example, and the oligonucleotides in claim 14. The restriction requirement and how it affects the examination of claim 1, for example, is set forth below.

Claims 1, 2, 13, and 15 link(s) the polymorphisms in claims 3-12 and the oligonucleotides in claim 14. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claims 1, 2, 13 and 15. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104. Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312. Applicant(s) are advised that if any claim(s) including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional

application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The traversal that the restriction requirement between polymorphisms and oligonucleotides should be an election of species has been thoroughly reviewed but was not found persuasive as the nucleic acid molecules comprising each polymorphism are structurally and functionally distinct. A search for each polymorphism is not coextensive. Searching must be conducted not only in sequence databases such as Genbank, but in the patent and non patent literature as well as polymorphism databases such as dbSNP because sequence databases, such as Genbank, do not normally provide information on SNPs. A complete search for each polymorphism is not coextensive. Search and examination of more than one of the polymorphisms for patentability presents a serious burden on the office. The response's assertion that the claimed polymorphisms are all associated with breast cancer (it is noted that the instant specification asserts an association with melanoma, not breast cancer) is not found persuasive. As can be seen in tables 7- 10, the polymorphisms are not statistically associated with melanoma in woman, and only subset show a p value of less than .05 in males (table 9). The polymorphisms are structurally and functionally distinct. Further, each oligonucleotide listed in claim 14 is directed to oligonucleotides used to detect distinct polymorphisms. These oligonucleotides themselves are structurally and functionally distinct.

The requirement is still deemed proper and is therefore made FINAL.

2. As noted in the restriction requirement, at page 4, 2nd para, any claim specifically drawn to a non elected sequence or variant will be withdrawn from consideration. The restriction requirement also notes that if only one polymorphism is elected, claims to two or more polymorphisms will be withdrawn from consideration as drawn to non elected inventions. Accordingly, claims 5-9, and 11-12 are withdrawn from consideration as drawn to non elected inventions. An action on the merits of claims 1-4, 10, and 13-15 follows.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Compact Disc Submission

4. Portions of this application are contained on compact disc(s). When portions of an application are contained on a compact disc, the paper portion of the specification must identify the compact disc(s) and list the files including name, file size, and creation date on each of the compact discs. See 37 CFR 1.52(e). Compact disc labeled "CRF" is not identified in the paper portion of the specification with a listing of all of the files contained on the disc. Applicant is required to amend the specification to identify each disc and the files contained on each disc including the file name, file size, and file creation date.

5. This application contains compact disc(s) as part of the originally filed subject matter, but does not contain an incorporation by reference statement for the compact discs. See 37 CFR 1.77(b)(4). Applicant(s) are required to insert in the specification an incorporation-by-reference of the material on the compact disc(s).

Information Disclosure Statement

6. A portion of the information disclosure statement filed 7/21/2006 lists pending applications but fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. See MPEP 609.04 (a) (II). The IDS fails to comply with section 4 in relation to the pending applications for section 1 above.

"Pending U.S. applications that are being cited can be listed under the non-patent literature section or in a new section appropriately labeled. The list of information complying with the *format requirements of 37 CFR 1.98(a)(1)* and the identification requirements of 37 CFR 1.98(b) may not be incorporated into the specification of the application in which it is being supplied, but must be submitted in a separate paper."

The references filed in form PTO/SB/08a on 7/21/2006 have been considered.

Claim Objections

7. Claim 3 is objected to because of the following informalities: Claim 3 recites "is detected at position the one or more polymorphic variations are detected at one or more positions ...", which is grammatically incorrect. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-4, 10, and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to identifying any subject at risk of melanoma comprising detecting the presence or absence of one or more polymorphic variations in a) SEQ ID NO: 1, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 1, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by SEQ ID NO: 1, or d) any fragment of a, b, or c; wherein the nucleotide sequence contains a T at position 171429 of SEQ ID NO: 1, whereby the presence of the polymorphism is

indicative of the subject being at risk of melanoma. The claims are also broadly drawn to detecting one or more polymorphic variations in linkage disequilibrium with the polymorphism at position 146311 of SEQ ID NO:1, as well as any polymorphism at position 146311 of SEQ ID NO: 1.

The genus encompassed by the claims is a broad variable genus as discussed below. The claims encompass not only detection of any polymorphism in SEQ ID NO: 1, which the specification teaches is a BRAF nucleotide sequence, but in sequences which encode a polypeptide encoded by SEQ ID NO: 1, sequences which encode a polypeptide with 90% identity to a polypeptide encoded by SEQ ID NO: 1, as well as sequences comprising fragments of such. The claims therefore encompass detection of polymorphisms in a large genus of variants, mutants and homologs of SEQ ID NO: 1, from any source. However, the specification does not teach degenerate variants of SEQ ID NO:1, nor does the specification teach any homologs of SEQ ID NO: 1 which encode a polypeptide with 90% identity with a polypeptide encoded by SEQ ID NO: 1. The specification does not teach any polymorphisms whatsoever, in any variants, mutants or homologs encompassed by sections b-d of claim 1 or any polymorphisms in any other species -let alone any SNPs that are statistically associated with melanoma. The claims also broadly encompass identifying SNPs in any subject, which encompasses any species, however the specification only teaches the identification of 12 SNPs in SEQ ID NO: 1 in humans (tables 7-10) which is over 190 kb. Of these 12, on genotype analysis, none are statistically associated with melanoma in females (table 10), and only 6 have a p value of less than 0.05 in males (table 9).

The broad genus further encompasses detecting polymorphic variations that are in linkage disequilibrium with the elected polymorphic variation at position 146311 of SEQ ID NO: 1. At page 68, the specification teaches that positions 146311, 138875, 76799 and 68398 in SEQ ID NO: 1 are in strong linkage disequilibrium. However, in table 9, only the SNP at position 146311 has a p value of less than 0.05. The other three SNPs do not appear to be, based on single genotype analysis, associated with melanoma in males. None of the SNPS (table 10) appear to be associated with melanoma in females. Accordingly, the detection of a SNP within this region would not be predictably diagnostic of melanoma or risk of melanoma. It is clear from tables 9 and 10, that a SNP, by virtue of being in SEQ ID NO: 1 is not necessarily associated with melanoma. The specification provides no structure/function correlation between any particular SNP in linkage disequilibrium with the elected SNP that is diagnostic for melanoma risk. Although the specification asserts "males having an adenine at position 146311 of SEQ ID NO: 1 are predisposed to melanoma" (page 61, para 00213), as evidenced by the haplotypes at table 12, both the C and the A alleles occur in different genetic backgrounds. Additionally, the specification teaches that allelotyping failed at this position (table 7). Therefore, it is not clear that disease association for this SNP was validated at the genetic level (see page 61, para 00212, last sentence). The specification teaches that haplotypes CTTG and ATGA (first position of haplotype is position 146311) are both associated with melanoma risk in males, but not females (tables 14 and 15). However, both the C and the A allele are also found in non risk associated haplotypes. Therefore, it is clear that determination of either the C or the A allele at position 146311, alone, or any single allele in linkage disequilibrium with this

position, is not indicative of melanoma risk, in either males or females. However, the claims are broadly drawn to determination of a single position.

The current claims encompass detection in a large variable genus of nucleic acids which comprise polymorphisms in any region of the BRAF gene, surrounding region, or homolog from any source. The genus includes an enormous number of polymorphisms and mutations for which no written description is provided in the specification. The specification only teaches of 12 particular polymorphisms for which data is provided. However, as noted above, the data for each SNP is conflicting in males vs females, as well as with genotype analysis of each positions singly. Thus, applicant has express possession of only 12 particular polymorphisms in SEQ ID NO: 1 which show conflicting association in melanoma, in a genus which comprises hundreds of millions of different possibilities.

The broad variable genus is not represented by the particularly 12 named variants in table 4 of the specification for the reasons which follow. In the broadly claimed invention, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with melanoma is provided. However, no predictable correlation between the structural alterations of the 12 polymorphisms disclosed and melanoma is provided by the specification. The specification does not teach the function of polymorphisms of the BRAF "region" nor how their function, or lack of function, or altered function are predictably associated with melanoma. The specification teaches 12 SNPs (table 4) were found in SEQ ID NO: 1, but that only 6 particular positions exhibited a p value of less than 0.05, and the identity

of any particular "risk associated" allele is unclear. The specification provides no guidance that broadly "any" polymorphism in the encompassed nucleic acids would be predictable of melanoma association. It is further noted that the claims broadly encompass "any" polymorphic variation at the disclosed position (eg, elected position 146311 of SEQ ID NO: 1), but only teaches 2 out of 4 possible variations at each position (A/C at position 146311). The specification does not teach if a G or T would be statistically associated with melanoma nor does it provide any guidance as to whether the particular nucleotide variants even exist. The specification provides no guidance that any alteration, in any BRAF gene, in any subject, is diagnostic for increased risk for melanoma.

Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. Additionally, the specification provides no evidence that any SNP at such position, in either humans, or mice or dogs for example, provides a predictable association with melanoma. The polymorphisms shown are not representative of the genus of any polymorphism associated with melanoma because it is not clear which polymorphisms within a BRAF region would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the melanoma may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification provides no guidance that the specific alleles exist in other species, therefore, there is no teaching

or guidance as to the identity of alleles in linkage disequilibrium with recited alleles in other species. The specification fails to provide any teaching or guidance as to what the structure of phenotypically associated alleles would be in variants or homologs of SEQ ID NO: 1 in humans, or in BRAF variants or homologs in other species. Accordingly, the particularly disclosed variants are not representative of the large variable genus encompassed by the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention. However, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with

reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

10. Claims 1-4, 10, and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

The claims have been amended to recite "wherein the nucleotide sequence contains a thymine at position 171429 of SEQ IS NO: 1". The claims originally recited "wherein the polymorphic variation does not alter the valine at position 599 of the amino acid sequence set forth in figure 3B". The response points to SEQ ID NO: 1 for basis for the amendment. However, SEQ ID NO: 1 contains over 190kb and neither the specification nor the originally filed claims provide support for specifically designating position 171429 as a T in the variants and homologs encompassed by claim 1. The T at position 171429 is in the middle of a codon. Were this position to remain fixed as a T, other amino acid variants which are encompassed by the claims include Phe (TTT, TTC), Leu (TTA, TTG, CT, CTC, CTA, CTG), Ile (ATT, ATC, ATA), and Met (ATG). Accordingly, the amendments appear to introduce new matter into the claimed invention.

11. Claims 1-4, 10, and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to identifying any subject at risk of melanoma comprising detecting the presence or absence of one or more polymorphic variations in a) SEQ ID NO: 1, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 1, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by SEQ ID NO: 1, or d) any fragment of a, b, or c; wherein the nucleotide sequence contains a T at position 171429 of SEQ ID NO: 1, whereby the presence of the polymorphism is indicative of the subject being at risk of melanoma. The claims are also broadly drawn to detecting one or more polymorphic variations in linkage disequilibrium with the polymorphism

at position 146311 of SEQ ID NO: 1, as well as any polymorphism at position 146311 of SEQ ID NO: 1.

The nature of the claimed invention, therefore, requires the knowledge of predictive associations between any polymorphism in any of the recited nucleic acids, or any polymorphism in linkage disequilibrium with such, in any subject and a risk for melanoma.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that SEQ ID NO: 1 is a BRAF a nucleotide sequence (page 3). However, the specification does not teach which portions of SEQ ID NO: 1 are directed to the human BRAF gene, where the regulatory regions, such as the promoter, lie, and whether the sequence comprises the entire gene. The specification teaches that 12 polymorphisms were identified in the sequence (table 4) and teaches that allelotyping and genotyping analysis was conducted on Caucasian male and female subjects of German maternal and paternal descent (page 61). The specification teaches that analysis was undertaken for male and female cases with melanoma and for male and female controls not having cancer. The specification teaches that when allelotyping and genotyping results agreed, the SNP disease association was considered validated at the genetic level (page 61).

However, the claims broadly encompass detection in variants, mutants and homologs of SEQ ID NO: 1 (sections b-d of claim 1, for example), and the specification does not teach whether any SNPs are statistically associated with melanoma in such sequences. The claims are drawn not only to detection of any polymorphism in SEQ ID NO: 1, but in sequences which encode a polypeptide encoded by SEQ ID NO: 1, sequences which encode a polypeptide with

90% identity to a polypeptide encoded by SEQ ID NO: 1, as well as sequences comprising fragments of such. The claims therefore encompass detection of polymorphisms in a large genus of variants, mutants and homologs of SEQ ID NO: 1, from any source. However, the specification does not teach degenerate variants of SEQ ID NO: 1, nor does the specification teach any homologs of SEQ ID NO: 1 which encode a polypeptide with 90% identity with a polypeptide encoded by SEQ ID NO: 1. The specification does not teach any polymorphisms whatsoever, in any of the sequences encompassed by sections b-d of claim 1 or any polymorphisms in any other species. The claims also broadly encompass identifying SNPs in any subject, which encompasses any species, however the specification only teaches the identification of 12 SNPs in SEQ ID NO: 1 in humans (tables 7-10) which is over 190 kb. Of these 12, on genotype analysis, none were found to be statistically associated with melanoma in females (table 10), and only 6 have a p value of less than 0.05 in males (table 9).

The claims further encompasses detecting polymorphic variations that are in linkage disequilibrium with the elected polymorphic variation at position 146311 of SEQ ID NO: 1. At page 68, the specification teaches that positions 146311, 138875, 76799 and 68398 in SEQ ID NO: 1 are in "strong" linkage disequilibrium. However, in table 9, only the SNP at position 146311 has a p value of less than 0.05. The other three SNPs do not appear to be, based on single genotype analysis, associated with melanoma in males. None of the SNPS (table 10) appear to be associated with melanoma in females. Accordingly, the detection of a SNP within this region would not be predictably diagnostic of melanoma or risk of melanoma. It is clear from tables 9 and 10, that a SNP, by virtue of being in SEQ ID NO: 1 is not necessarily associated with melanoma. The specification provides no structure/function correlation between

any particular SNP in linkage disequilibrium with the elected SNP that is diagnostic for melanoma risk. Although the specification asserts "males having an adenine at position 146311 of SEQ ID NO: 1 are predisposed to melanoma" (page 61, para 00213), as evidenced by the haplotypes at table 12, both the C and the A alleles occur in different genetic backgrounds. Although the specification asserts "males having an adenine at position 146311 of SEQ ID NO: 1 are predisposed to melanoma" (page 61, para 00213), as evidenced by the haplotypes at table 12, both the C and the A alleles occur in different genetic backgrounds. Additionally, the specification teaches that allelotyping failed at this position (table 7). Therefore, it is not clear that disease association for this SNP was validated at the genetic level (see page 61, para 00212, last sentence). The specification teaches that haplotypes CTTG and ATGA (first position of haplotype is position 146311) are both associated with melanoma risk in males, but not females (tables 14 and 15). However, both the C and the A allele are also found in non risk associated haplotypes. Therefore, it is clear that determination of either the C or the A allele at position 146311, alone, or any single allele in linkage disequilibrium with this position, is not indicative of melanoma risk, in either males or females. The claims are broadly drawn to determination of a single position, however the specification provides no predictable correlation between any particular SNP in linkage disequilibrium with the elected SNP that is diagnostic for melanoma risk.

The specification provides no universal correlation that any SNP in any of the claimed nucleic acids would be associated with melanoma nor does it provide any way to predict which sequences within the broadly claimed sequences would be "melanoma associated". Of 12 disclosed SNPs, the specification teaches a p value of less than 0.05 in 6 positions, in males only.

Thus it is clear that "any" polymorphism in the encompassed nucleic acids would not be predictable of melanoma risk. It is further noted that the claims broadly encompass "any" polymorphic variation at the disclosed position (eg, elected position 146311 of SEQ ID NO: 1), but only teaches 2 out of 4 possible variations at each position (A / C at position 146311). The specification does not teach if a G or a T would be statistically associated with melanoma or treatment nor does it provide any guidance as to whether these particular nucleotide variants even exist.

Additionally, the specification provides no guidance as to how the SNP at 146311 (A/C), or any of the other 11 variants, singly or in haplotypes, function to provide for increased risk of melanoma. The specification provides no structure/function correlation between the disclosed SNPs and melanoma for the skilled artisan to be able to predict which other positions within the claimed sequences might be predictably associated with the claimed phenotypes. It is not clear if any other variant at that position would have the same effect.

It is not known whether the C/A polymorphism at position 146311 exists in other variants or homologs or other mammalian genes or what other variant positions would be in another gene or whether a polymorphism would have the same effect in another gene, or what the identity of that polymorphism might be. Therefore, the skilled artisan would be unable to predictably correlate any other structural change in any other region of BRAF in any other species. The elected allele could be part of a melanoma-associated haplotype, however the causative mutation is not necessarily one of the SNPs taught in the specification. The causative mutation could be in a gene thousands of nucleotides away, however the specification provides no indication of what this allele might be.

The specification provides no predictable association that any alteration, in any BRAF gene, in any subject, is diagnostic for increased risk of melanoma. No common element or attributes of the sequences are disclosed which would permit selection of sequence polymorphisms as diagnostic for an increased risk of melanoma. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with melanoma is provided. Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. However, the specification provides no evidence that any polymorphic variation at such positions, in either humans, or mice or dogs for example, provides a predictable association with melanoma. The polymorphisms shown are not predictive of the genus of any polymorphism associated with melanoma because it is not clear which polymorphisms within "any" BRAF sequence would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the detected melanoma association may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of polymorphisms of SEQ ID NO: 1, nor how their function, or lack of function, or altered function are predictably associated with melanoma.

The state of the prior art and the predictability or unpredictability of the art:

At the time the invention was filed, the prior did not teach the function or biological activity of polymorphisms in BRAF with regard to melanoma. The specification demonstrates the unpredictability of this invention since 6 of the 12 identified SNPs in SEQ ID NO: 1 were not statistically significant in males and none of the 12 were statistically significant in females, as well as the number of haplotypes which are not statistically significant in males or females, and do not appear to be melanoma associated given the data in the specification. Thisted et al (see galston.uchicago.edu/~thisted/, pages 1-5) notes that "It has become scientific convention to say that p-values exceeding .05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their effect (see page 5).

Further, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Hacker et al; Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate

SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789).

With regard to BRAF, Laud (Laud et al; Cancer Research, vol. 63, pages 3061-3065; 2003) teaches that BRAF is unlikely to be a melanoma susceptibility gene. Laud teaches screening at the germline level for mutations in independent melanoma prone families, and patients with multiple primary melanoma without a familial history (see abstract). Laud teaches that 13 variants were identified, including 4 which were silent and 9 which occurred in introns. Laud teaches that none of the variants segregated with melanoma in the 11 melanoma families studied and that there was no significant difference in the frequency of heterozygotes for BRAF variants between melanoma and controls. Further, Jackson (Jackson et al; Cancer Epidemiology, Biomarkers, and Prevention; vol. 14, 2005, pages 913-918) teaches that somatic mutations of BRAF had been identified in both melanoma tumors and benign nevi, but that germ line mutations had not been identified as causal in families predisposed to melanoma (see abstract). Jackson teaches that a recent study (referring to Meyer et al; Journal of Carcinogenesis, vol 2, 2003, pages 1-5, which appears to teach portions of the data in the instant specification) suggested that a BRAF haplotype was associated with risk of sporadic melanoma in men (see abstract). Jackson teaches that this observation needed to be assessed in another population. Jackson teaches screening a 1 KB region upstream of the BRAF start codon, which is thought to contain the promoter, for variants (page 913, col 2, 2nd full para). Jackson teaches 6 variants were found and that a promoter insertion/deletion, which is in linkage disequilibrium with the intron 11 SNP (rs1639679) at position 146311 of SEQ ID NO: 1, was analyzed in populations from the UK, for melanoma susceptibility, but that no statistically significant difference in either

genotype or allele frequencies between cases and controls overall or between male and female cases was found (see abstract). Further, Jackson teaches that there was "no difference in the prevalence of the intron 11 polymorphism [position 146311 of SEQ ID NO: 1] associated with the H2 haplotype between cases and controls" and that "no difference as seen in the familial cases, where there was a higher allele frequency in males compared with females. This result is only just significant (P=0.05) and may be due to chance, especially as the allele frequency estimated from the female familial cases is the lowest of the sample series that we studied (table 3). In addition, we have found no evidence for an association between a common promoter insertion/deletion (present in the haplotype H2 described by Meyer) and melanoma risk". Accordingly, the art confirms the unpredictability of associating SNPs, including those in BRAF and including those in linkage disequilibrium, with disease susceptibility including in different populations, even for SNPs which have been found to be associated in other studies.

In the instant case, the specification only provides information that the A/C variant exists in humans and is associated with melanoma in certain haplotypic backgrounds in males only, but provides no guidance that it, or any other alleles which either are or are not in linkage disequilibrium, in SEQ ID NO: 1, have any effect whatsoever on the expression or activity of human BRAF or the broadly claimed sequences.

The level of skill in the art:

The level of skill in the art is deemed to be high, however the experimentation required to practice the broadly claimed invention is even higher.

The quantity of experimentation necessary:

The quantity of experimentation in this area is extremely large as it requires analysis of each position in SEQ ID NO: 1, as well as the broadly encompassed mutants, variants, and homologs encompassed by the claims to determine whether any alteration at each position is associated with melanoma and to identify which variations are predictably associated with melanoma in any subject. As neither the art nor the specification provide guidance as to which alterations at positions throughout BRAF are predictably associated with melanoma, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each possible alteration in the broadly claimed genomic sequences, including SEQ ID NO: 1, represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success.

In order to practice the invention as claimed, one would first have to establish that a predictive relationship exists between the disclosed polymorphisms and melanoma. Further, the scope of many of the claims requires knowledge of an association between all mutations in any BRAF gene and melanoma in humans or any species. Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation with a large number of patients with melanoma and controls, to determine mutations that share a predictive correlation with melanoma.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
> (f) he did not himself invent the subject matter sought to be patented.

13. Claims 1, 2, 13, and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Stratton (Stratton et al; US PGPub 2004/0096855). Stratton teaches detecting mutations in B-RAF for diagnosis of predisposition to cancer in human subjects (see abstract). With regard to claim 1, Stratton teaches detecting a G1394C mutation which encodes a G465A mutation in B-RAF in melanoma (see table 1, page 14). Stratton teaches detecting mutations using PCR (page 9, para 0148 and 0150).

14. Claims 1-4, 10, 13, and 15 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. This is an inquiry under 35 USC 102(f). There appears to be an inconsistency as Myer et al (Journal of Carcinogenesis, vol. 2, 2003, pages 1-5), teaches the at risk alleles and haplotypes taught in the instant specification in humans in BRAF, as well as melanoma disease risk in men, in a Caucasian population of German descent (page 4), as well as methods of detecting polymorphisms in claim 13 (page 4, col. 2). The data in the specification and that in the paper appear to be the same. However, the inventorship of the

instant application and the authorship of the paper are entirely different. MPEP 2137 states: "...it is incumbent upon the inventors named in the application, in reply to an inquiry regarding the appropriate inventorship under subsection (f), ...to provide a satisfactory showing by way of affidavit under 37 CFR 1.132 that the inventorship of the application is correct in that the reference discloses subject matter invented by the applicant rather than derived from the author or patentee notwithstanding the authorship of the article or the inventorship of the patent. *In re Katz*, 687 F.2d 450, 455, 215 USPQ 14, 18 (CCPA 1982) (inquiry is appropriate to clarify any ambiguity created by an article regarding inventorship, and it is then incumbent upon the applicant to provide "a satisfactory showing that would lead to a reasonable conclusion that [applicant] is the...inventor" of the subject matter disclosed in the article and claimed in the application).

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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